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ORIGINAL ARTICLE

Clinical Characteristics of Nosocomial Rotavirus Infection in Children in Taiwan

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Background/Purpose: The aim of this study was to determine the incidence and clinical characteristics of nosocomial rotavirus infection (NRI) among hospitalized children.
Methods: We collected data of children in the Department of Pediatrics with positive stool rotavirus antigen tests. Cases of an admission diagnosis of acute gastroenteritis or a positive stool rotavirus antigen test within 3 days of admission, representing community-acquired infections, were excluded. Both VP4 and VP7 genotyping of the rotaviruses was done.
Results: There were 98 patients who met the inclusion criteria during the 3-year period. The incidence density was 0.58 per 1000 patient-days in our series. Among these patients, 59 (60%) had underlying diseases. The intermediate intensive care unit had the highest incidence density (2.8 per 1000 patient-days). Overcrowding of the care unit, inappropriate hand hygiene, and inadequate isolation and cohorting predisposed to the high rate. Genotypes among 79 (80%) rotaviruses tested showed that 42% belonged to the novel genotype, G9P[8].
Conclusion: NRI may cause significant morbidity in hospitalized children, especially young infants and those with underlying diseases. Infection control with hospital surveillance, strict isolation and cohort care should be adopted to prevent the spread of rotavirus among special care units. [*J Formos Med Assoc* 2008;107(10):791–797]

Key Words: child, nosocomial infections, pediatrics, rotavirus

Rotavirus, a 70-nm particle with double-stranded RNA, was first reported in 1973 to have high a causal relationship with childhood diarrhea.[1] It was highly contagious with a fecal-oral route of transmission and was possibly airborne.[2] Rotavirus gastroenteritis was the leading cause of severe diarrhea in children and carried a heavy burden both medically and economically. The cumulative age distribution of rotavirus infection showed that almost all children in Asia had been infected before the age of 5.[3] Rotavirus gastroenteritis claimed 600,000 deaths annually worldwide[4] and there has been no specific treatment. The surveillance data of the Centers for Disease Control, Taiwan, showed that rotavirus was the leading cause (43%) of gastroenteritis among children under the age of 5 in Taiwan during 2001–2003.[5] Hospitalized children with rotavirus gastroenteritis were a potential reservoir for its spread in the wards. Unpredictable episodes of the nosocomial infection led to prolonged hospital stay, increased medical costs and posed a threat to hospitalized

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children, especially those with underlying diseases. Outbreaks of rotavirus gastroenteritis are common in the setting of pediatric health care units. In developed countries, nosocomial rotavirus infection (NRI) was reported to represent 27% (range, 14–51%) of rotavirus infections, which was quite similar to the figure (32%) for developing countries.[6] However, there are limited data on the clinical and epidemiologic features of NRI in Asia.[7,8] This study aimed to determine the incidence and clinical characteristics of NRI in Taiwan.

Methods

We reviewed the medical charts of hospitalized children with positive stool rotavirus antigen tests between December 2001 and November 2004, based on the database of the hospital virology laboratory. The National Taiwan University Hospital, situated in northern Taiwan, is a medical center responsible for primary to tertiary care and is a 2500-bed university-affiliated hospital. The Department of Pediatrics is a 218-bed multifunctional and multidisciplinary unit in the hospital. Children with an admission diagnosis of acute gastroenteritis or a positive stool rotavirus antigen test within 3 days of admission were defined to have community-acquired rotavirus infections (CARI). Children who developed gastrointestinal symptoms from 3 days after admission to within 2 days of discharge were defined to have NRI.

The health care units enrolled in this study included general pediatric wards, the hematology/oncology ward, intermediate intensive care unit (ICU), pediatric ICU (PICU), observation room for neonates, observation room for young infants, neonatal ICU (NICU), baby room and a satellite ward off the main building. The intermediate ICU was the bridge between the PICU and the general pediatric wards. Patients in the intermediate ICU were mainly infants with congenital heart disease or neurologic disorders. The information department provided the total number of hospital days of all the health care units during this period. The incidence density of NRI was calculated by dividing the case numbers of NRI by the total hospital days in the specific ward.

Fever was defined as a body temperature higher than 38°C. For those who were intubated with a nasogastric tube, vomiting was defined as the increase in amount of drainage from the tube after feeding. Diarrhea was defined as fecal amounts of more than 10 g/kg/day in infants or more than three passages of looser-than-usual stool in 1 day in children. If the characteristics or the frequency of stool passage could not be clearly defined, the medical chart was reviewed. Stool occult blood was defined as at least 2++.

The rotavirus antigen was detected from stools by monoclonal antibody incorporated enzyme-linked immunosorbent assay (ELISA) (Rotaclone; Meridian Diagnostic, Cincinnati, OH, USA). Samples tested positive for rotavirus antigen were stored at −70°C before further molecular analysis. RNA polyacrylamide gel electrophoresis and reverse transcriptase polymerase chain reaction with nucleotide sequencing were done for further genotyping of the VP4 (P type) and VP7 (G type) genes.[9,10]

Data were statistically analyzed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) for Windows. Categorical variables were assessed for statistical significance by the χ^2 test. The Mann-Whitney *U* test was used for continuous variables with skewed sample distribution. A p value below 0.05 was considered statistically significant.

Results

Ninety-eight patients met the inclusion criteria of NRI during the 3-year period. Fifty-eight were boys and 40 were girls. Their ages ranged from 11 days to 226 months with a median of 8 months. Forty percent of NRI occurred in children younger than 6 months of age, whereas 12% occurred in those over 5 years of age (Figure 1A). During the 3-year period, there were a total of 4515 stool specimens subjected to the rotavirus antigen test and 843 (19%) of these were positive. Among

those with positive tests, 510 (60%) were inpatients while the remaining 333 (40%) were outpatients. In the same period, there were 604 children hospitalized with acute gastroenteritis (ICD-9-CM) and most of them were tested for rotavirus antigen. A sentinel surveillance study during this period showed that 43% of the inpatients with gastroenteritis were rotavirus-related.[5] NRI cases ($n=98$) represented 19.2% of all the cases of rotavirus gastroenteritis requiring hospitalization ($n=510$) and 49% of all nosocomial gastroenteritis. The NRI case numbers during the 3-year period were 34, 26 and 38 per year.

The clinical symptoms are summarized in the Table. Fever (80%, $n=78$) and diarrhea (97%, $n=95$) were the most common symptoms. Fever

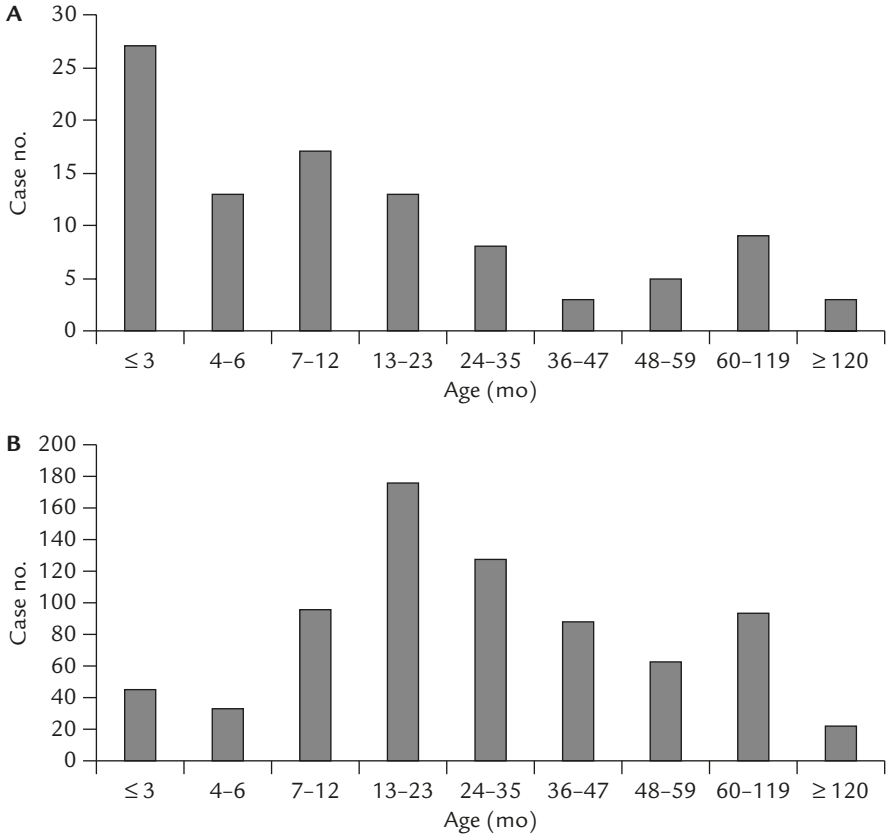

Figure 1. Age distributions of: (A) nosocomial rotavirus infection (NRI); (B) community-acquired rotavirus infection (CARI).

Table. Clinical manifestations of nosocomial rotavirus infection*

Symptoms/signs	Total patients ($n=98$)		Children with underlying disease ($n=59$)		Children without underlying disease ($n=39$)	
	n (%)	Duration*	*n* (%)	Duration*	*n* (%)	Duration*
Fever	78 (80)	1 (1–10)	44 (75)	1 (1–10)	34 (87)	1 (1–2)
Vomiting	58 (59)	1 (1–6)	35 (59)	2 (1–6)	23 (59)	1 (1–4)
Diarrhea	95 (97)	4 (1–14)	57 (97)	4 (1–14)	38 (97)	3 (1–11)
Stool with occult blood	14/52 (27)	NA	10/27 (37)	NA	4/25 (16)	NA
Onset after admission (d)	9 (3–319)		18 (3–319)		7 (3–36)	

**Duration of symptoms presented as median (range) in days. NA = not available.*

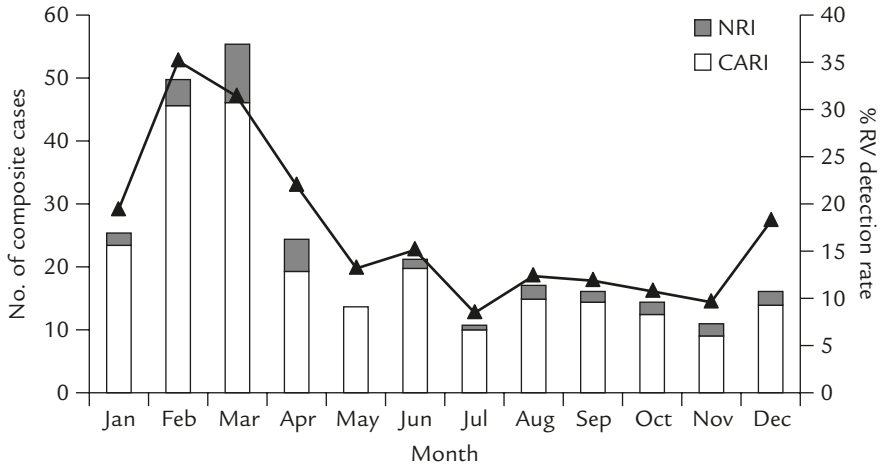

Figure 2. Seasonality of nosocomial rotavirus infection (NRI) and community-acquired rotavirus infection (CARI). The y-axes show the number of composite monthly cases and composite monthly percentages of rotaviral detection.

and vomiting were both of short duration (median duration 1 day) while diarrhea lasted for a median of 4 days. There were three children without diarrhea but all had fever and vomiting. Three children developed seizures; however, all of them had comorbid diseases: two had bacterial meningitis and the other had a preceding head injury. Among the children with NRI, 59 (60%) had underlying diseases, which included congenital heart disease (40.7%), malignancy (15%), neurologic disorders (13.6%), metabolic or endocrine disorders (8.5%), upper airway anomalies (6.8%), prematurity (5%), immunodeficiency (3.4%), and gastrointestinal disorders (3.4%).

Infants younger than 6 months of age had fewer febrile episodes (67.6% *vs.* 87.9%, $p = 0.021$) and a shorter duration of fever during rotavirus infection (1.46 ± 1.37 days *vs.* 1.98 ± 1.76 days, $p = 0.016$). Nevertheless, the frequencies of vomiting (60%) and diarrhea (93%) were similar to those of older children (59%, 100%) and were not associated with the age of the patients. Almost all received parenteral fluid rehydration.

The median time of the onset of NRI was 9 days. Five patients (5%) developed diarrhea after they were discharged from hospital and required hospitalization again. Three cases had concomitant sepsis and two of these may have been central venous catheter-related. Twenty-seven percent of cases were found to have occult blood in the stool. One patient with combined immunodeficiency had two episodes of NRI separated by 6 months; both episodes had a prolonged shedding of rotavirus for 1 month.

Rotavirus gastroenteritis occurred all year round with some yearly variations during the 3-year study period (data not shown). The peak season of NRI, coinciding with that of CARI, was between February and April (Figure 2). The average incidence density was 0.58 per 1000 patient-days, with monthly incidences varying between 0 and 3.3 per 1000. The intermediate ICU had the highest incidence of NRI (2.8 per 1000 hospital-days), followed by the observation room for younger infants (0.8 per 1000 hospital-days), general wards (0.34–0.68 per 1000 hospital-days), PICU (0.38 per 1000 hospital-days), hemato-oncology ward (0.27 per 1000 hospital-days), NICU and the observation room for neonates (0.13–0.15 per 1000 hospital-days). The incidence could reach as high as 4.77 per 1000 hospital-days between February and April.

The genotypes of the 79 (80%) rotaviruses showed that G9P[8] was the most common (42%), followed by G1P[8] (20%), G3P[8] (19%), G2P[4] (18%) and G1P[4] (1%). Further analysis of the episodes in the intermediate ICU identified two outbreaks during the study period (Figure 3), the first in March 2003 with G3P[8] in eight of the nine cases and the other in November 2004, with all five cases being G3P[8].

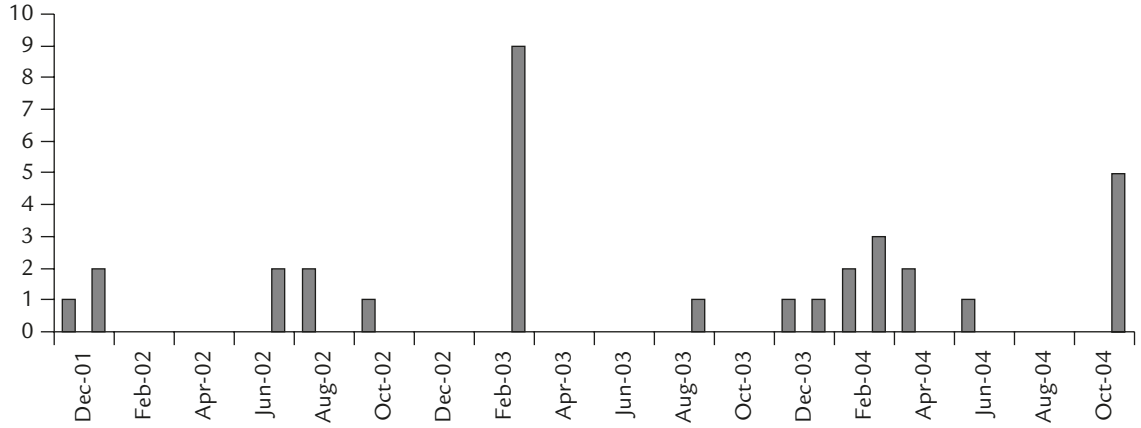

Figure 3. Nosocomial rotavirus infection episodes in the intermediate intensive care unit during the study period.

Discussion

It has been suggested that rotavirus infections are more severe in children with immunodeficiency.[11,12] Children with or without underlying diseases in our series had similar rates and durations of symptoms, including the proportion of stools with occult blood ($p = 0.121$). However, further investigation was needed due to the small case numbers in this study.

There was a major difference between the ages of cases with NRI and CARI. Children with NRI tended to be younger compared with CARI. There were more children younger than 6 months of age in the NRI group than in the CARI group (40% *vs.* 10%, $p < 0.001$). Although there might be false-positive results of ELISA reactions in neonates,[13] most (85%) rotaviruses in those younger than 6 months of age with NRI were symptomatic and genotype testing was positive. The intermediate ICU, to which 40% of NRI cases belonged, mainly accommodated infants younger than 4 months of age, especially those with underlying diseases. They needed frequent medical care and tended to have a prolonged hospital stay, which predisposed to secondary NRI.[8,14] Both factors contributed to the younger age in the NRI group. Factors favoring NRI in the intermediate ICU were overcrowding in the environment, a high patient turnover rate, family visitation, inadequate isolation facilities, shortage of nursing staff and incomplete enforcement of hand hygiene and cohorting.[15] Compared with older children, infants less than 6 months of age had no fever or a shorter duration of fever during rotavirus infection. Nevertheless, children with NRI, regardless of age, experienced high rates of vomiting and diarrhea in our study. Management such as changes in feeding, culture for possible bacterial sepsis, and parenteral rehydration still needed to be instituted.

Human rotavirus, a double-stranded RNA virus without a lipid envelop, can survive in the environment for several days.[16] The infectivity titers of rotaviruses could be reduced by a 60% ethanol solution or other detergents by > 3 logs in 1 minute.[17] However, children with rotavirus diarrhea may excrete up to 10^{12} infectious particles/mL of stool and the infective quantity in a child could be as few as 10 particles.[18] Rotaviruses remained infectious in susceptible hosts when improper sanitation occurred. Previous studies have demonstrated some risk factors associated with NRI, including a contaminated environment and fomites,[19] prolonged stay in hospital,[8,20] ungloved nasogastric feeding,[21] and lack of breast feeding.[22,23] It was also noted that infected medical personnel could be asymptomatic but shed and spread the rotavirus insidiously.[24] The control and prevention of NRI was difficult because of insufficient hand hygiene of health care providers,[25] inadequate isolation and cohorting,[15] frequent asymptomatic rotavirus shedding in young children,[26] prolonged shedding in immunocompromised patients, and even the potential route of

airborne transmission.[27] However, a study conducted in a US pediatric hospital showed that a vigorous hand washing hygiene program reduced the rate of NRI from 5.9 to 2.2 episodes per 1000 pediatric hospitalizations.[28] The benefits of probiotics[29] and changing diapers with gloves remain controversial.[30]

Surveillance and monitoring of the genotypes of the circulating rotaviruses could offer valuable information about molecular epidemiology and vaccine development. The most common genotype in this study was G9, which could be effectively protected against with currently available vaccines.[31,32] Recent surveillance data from northern Taiwan also identified G1, G2, G3 and G9 as the most prevalent genotypes from 2004 to 2006, and pinpointed the roles of other enteric viruses or mixed infections.[33] Given the fact that 40% of nosocomial cases occurred before 6 months of age, however, the impact of rotavirus vaccine on NRI needs careful evaluation.[34]

There are two major limitations of this study. First, the cases were reviewed retrospectively. The incidence density might have been underestimated as some infections might have been asymptomatic and escaped clinical diagnosis without appropriate laboratory surveillance. Furthermore, as high as 15% of rotavirus infections might not manifest until discharge from hospital.[35] Prospective laboratory-based surveillance was considered cost-effective in a pediatric hospital, even in non-epidemic seasons.[36] Second, this study was done in a tertiary medical center in Northern Taiwan. As such, selection bias was a possibility. A prospective, island-wide multicenter surveillance of nosocomial rotavirus infections is needed.

In summary, nosocomial rotavirus infections can cause significant morbidity in hospitalized patients. Children younger than 6 months of age, especially those with underlying diseases, are more susceptible to nosocomial rotavirus infections and have significant morbidity. The impact of a rotavirus vaccine on relieving the burden of nosocomial rotavirus infections awaits further investigation. The survey of circulating rotaviruses both in hospitals and in the community should be continued in order to better understand the epidemiology of rotavirus infection.

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